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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/628,494	07/28/2000	Emmanuel Mignot	HPZ-017	3784

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EXAMINER
SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/628,494	MIGNOT, EMMANUEL	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *06 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-8,10-12 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-8, 10-12, and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 July 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Currently, claims 1-3, 6-8, 10-12, and 45 are pending in the instant application. Claims 5, 9, and 38-44 were canceled. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are newly applied to the claims, necessitated by amendment. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

New Grounds or Objection and Rejection

Claim Objections

2. Claims 6 and 7 are objected to because of the following informalities: Claims 6 and 7, as amended, each recite "wherein the polymorphism *in* indicative..." As this recitation is not grammatically correct, it appears that the word "in" is misspelled and should be --is--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 6-8, 10-12, and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining a predisposition to

narcolepsy in canines by detecting a deletion of exon 4 or exon 6 of the hypocretin 2 receptor, does not reasonably provide enablement for detecting a predisposition to any sleep disorder, or narcolepsy, in any subject by detecting any polymorphism in a hypocretin receptor 2 gene which causes an alteration in activity of a hypocretin receptor encoded by the gene, or methods dependant therefrom wherein, in the alternative, the disorder is any sleep disorder that is characterized by increased wakefulness or decreased wakefulness, or wherein the individual is human or canine, or detecting any polymorphism within a genomic region between markers 26-8 and 530-3 of canine chromosome 12, or wherein the polymorphism is any polymorphism in exon 4 or exon 6 of the hypocretin receptor 2 gene, or encodes any truncated HCRtr2 transcript. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are broadly drawn to detecting a predisposition to any sleep disorder in any subject (encompasses any species) caused by any polymorphism in a hypocretin receptor 2 gene, wherein the polymorphism causes an alteration in the activity of a hypocretin receptor encoded by the gene. The claims are also broadly drawn to detecting a polymorphism that is anywhere between markers 26-8 and 530-3 and wherein the polymorphism is any polymorphism in exon 4 or exon 6 of the hypocretin receptor 2 gene, or encodes any truncated HCRtr2 transcript. The specification defines "polymorphism" to refer to a marker that is distinguishably different as compared to an analogous region from a subject of the same species (p. 13), thus the term encompasses deletions and insertions, as well as single nucleotide polymorphisms. The specification further defines "hypocretin-related disorder" and "disorder caused by an alteration in hypocretin receptor activity" as a disorder that is caused by an increase or decrease in binding

of hypocretin relative to that found in an unaffected subject. Further the specification asserts that an increase or decrease in hypocretin receptor activity can be caused by increased or decreased levels or availability of hypocretin ligand, alterations in a hypocretin receptor that affect the binding affinity of the receptor for hypocretin, and alterations in the hypocretin polypeptide that affect its binding affinity to a hypocretin receptor (p 11). Therefore the claims broadly encompass any mutation or polymorphism in a hypocretin receptor 2 gene, which encompasses polymorphisms in coding as well as non coding sequences that are not limited to genomic or cDNA for hypocretin receptor 2, and also include any sequences that affect regulation of hypocretin ligand binding or hypocretin receptor.

While the claims broadly encompass any sleep disorder, or more specifically any sleep disorder characterized by increased or decreased wakefulness, the specification has only taught that deletions in exon 4 or exon 6 in the hypocretin 2 receptor (pp 53, and 55 of the specification) is associated with narcolepsy in canines while a decreased level of hypocretin 1 ligand is associated with narcolepsy in humans. The specification provides no working examples that either the mutations in hypocretin receptor 2 or decreased levels of hypocretin 1 ligand is associated with any other sleep disorder, such as any sleep disorder characterized by increased or decreased wakefulness. Further, Aldrich (Neurology, vol. 50 suppl, pp s2-s7, 1998) teaches that while sleepiness can be a useful though not a definitive diagnostic tool, sleepiness, defined as a propensity to fall asleep easily in relaxed or sedentary situation, occurs mainly in sleep disorders and must be distinguished from fatigue and tiredness, which denote a lack of energy, motivation, or strength and which may occur with sleep disorders as well as with a variety of systemic and psychiatric disorders (see p. S2, col. 2, last para). Aldrich further teaches that daytime sleep

attacks, which are episodes of daytime sleep that occur without warning, are not specific for narcolepsy and that they may occur in association with any disorder that leads to severe chronic sleepiness (p. S3, col 1, 1st full para). Therefore, while sleep disorders such as sleep apnea, or idiopathic hyperinsomnia, may share a common symptom with narcolepsy, neither the specification nor the art teach an association between any polymorphism in either of the hypocretin receptors or hypocretin levels and these disorders. Further, neither the specification or the art provide any teaching of the affect of either the polymorphisms in hypocretin receptor 2 or decreased levels of hypocretin 1 on any of the symptoms of narcolepsy, nor how these aberrant mutations or levels cause narcolepsy such that the skilled artisan would be able to establish a predictable correlation that the association of narcolepsy with the aberrant mutations or levels taught in the specification are also associated generally with any sleep disorder, or any sleep disorder characterized by increased or decreased wakefulness, or disorders such as sleep apnea, idiopathic hyperinsomnia, etc. The recitation of the broad category of "sleep disorders" represents a heterogenous group of disorders whose causes are not well understood and whose association to narcolepsy is also unknown. To practice the invention as broadly as it is claimed the skilled artisan would have to perform a study which included a large number of different sleep disorders, screen subjects with these disorders as well as controls for any mutation in any hypocretin receptor 2 gene that altered the activity of hypocretin receptor 2 to determine if polymorphisms that affect hypocretin receptor activity are associated with these disorders. Because neither the specification nor the art provide any predictable correlation between mutations or polymorphisms which affect hypocretin receptor activity and any disorder, such a study would require mainly trial and error analysis the results of which are unpredictable.

The claims also broadly encompass detecting a predisposition to any sleep disorder in any subject by detecting any polymorphism *in* exon 4 or exon 6 of the hypocretin receptor 2 gene, however the specification has only taught that mutations leading to deletions of exon 4 or exon 6 of canine hypocretin receptor 2 (pp 53, and 55 of the specification) is associated with narcolepsy in canines. These aberrations are not predictably representative of the large number of polymorphisms which would be expected affect hypocretin receptor 2 activity in some way and potentially lead to narcolepsy encompassed by the claimed invention. While the deletions of exon 4 and exon 6 in hypocretin receptor 2 are associated with narcolepsy in canines, it is unclear from the teachings in the specification how these mutations affect hypocretin receptor activity such that narcolepsy results. The specification teaches that a large number of polymorphisms in hypocretin as well as hypocretin receptors 1 and 2 in humans were screened for an association with narcolepsy, but that none was found (p 61). Therefore, to practice the invention as broadly as it is claimed, the skilled artisan would have to screen both canine and human hypocretin receptor 2 to be able to determine which mutations cause an alteration in activity of hypocretin receptor 2 that lead to narcolepsy, or any sleep disorder. As the specification teaches that a large number of polymorphisms, which includes polymorphisms that resulted in codon changes, were not associated with narcolepsy, such an analysis would require trial and error manipulations, the results of which are clearly unpredictable as exemplified by the teachings in the specification. Such analysis is therefore considered undue.

Response to Arguments

The response traverses the rejection. The response asserts that the amendments to the claims obviate the rejection set forth in the previous office action because the specification contains ample teaching of how to make and use the claimed invention as well as working examples which describe the identification of the polymorphisms used in the methods of the invention. The response asserts that applicant's have shown that in both canines and humans, a defect in the hypocretin system is associated with sleep disorder. The response asserts that the system is disrupted either due to a defect in a hypocretin receptor that affects production of a full-length functional peptide (for example in canines) or a defect in a hypocretin ligand (mutation disclosed in examples 5-6), the subject is likely to suffer from a sleep disorder or narcolepsy. These arguments have been thoroughly reviewed but were found unpersuasive for the following reasons.

Firstly, with regard to the polymorphisms shown in the specification: in canines, the specification has shown that mutations in canine hypocretin receptor 2 gene which lead to deletions of exon 4 or exon 6 and result in truncated receptors are associated with narcolepsy. However, the specification has not demonstrated what activity or activities of this receptor were affected, or to what degree, to be able to predictably determine what other polymorphisms would cause similar affects of the hypocretin receptor 2 and be associated with narcolepsy. As stated in the previous office action, the term polymorphism can encompass insertions, deletions, and single nucleotide polymorphisms. However, neither the specification, nor the prior art demonstrate either the affect of the mutations shown in canines on the activity of the hypocretin receptor 2, or how such change in activity is associated with narcolepsy, in canines or any other

organism, including humans, such that the skilled artisan would be able to predictably correlate what other mutations in hypocretin receptor 2 would have the same affect. Furthermore, even if such an affect were shown for the deletion of a complete exon, neither the specification nor the art teach what polymorphisms leading amino acid changes within the deleted exon, for example, would have the same alteration in activity as the deletion of a complete exon. The unpredictability of associating any polymorphism, including polymorphisms which lead to codon changes that would be expected to alter the activity of the hypocretin receptor 2 in some way, is exemplified by the specification which teaches that a number of polymorphisms were detected in both hypocretin receptors 1 and 2 in humans, including ones that lead to amino acid changes, and yet none were associated with narcolepsy, let alone any sleep disorder in humans (see example 5, and table 2: pp 62-63, in the specification). The specification expressly teaches, for example, that a polymorphism that caused a threonine to isoleucine change at exon 7 of the hypocretin receptor 2, wherein a threonine or serine is normally conserved at that position in hypocretin receptors 1 and 2, was not found to be associated with sleep disorders even though that mutation would be expected to disrupt a phosphorylation site in the C terminal region of hypocretin receptor 2 and lead to dominant effects. The specification concludes that due to the pattern of inheritance, this substitution is probably benign (see p. 65, lines 12-21).

In addition, with regard to the single mutation associated with narcolepsy in humans, it is noted that the mutation is in the hypocretin ligand, whereas the claims are directed to mutations in hypocretin receptor 2. While the mutation in the signal sequence of the hypocretin ligand appears to be associated with narcolepsy, neither the specification nor the art teach how or where a mutation in hypocretin receptor 2 would lead to the same or a similar effect such that the

skilled artisan could predictably correlate which mutations in hypocretin receptor 2 were associated with any sleep disorder, or narcolepsy specifically. Therefore, while the mutation in the hypocretin ligand suggest that if the hypocretin system is disrupted, the subject is predisposed to narcolepsy, the claims are directed to alterations that affect the activity of the hypocretin receptor 2, and based on the unpredictability with regard to which mutations will affect hypocretin receptor 2 activity such that the hypocretin system is disrupted, or which hypocretin receptor 2 activity is associated with narcolepsy, the skilled artisan would have to perform trial and error analysis to establish which mutations are predictably correlative with narcolepsy or any sleep disorder, to practice the invention as broadly as it is claimed. The results of such analysis are unpredictable, however. Further, with respect to sleep disorders, it is noted that the mutations exemplified in the specification were associated with narcolepsy and not sleep disorders in general. However, as stated in the previous office action, "sleep disorders" represents a heterogenous group of disorders whose causes are not well understood and whose association to narcolepsy is also unknown. Aldrich teaches that daytime sleep attacks, which are episodes of daytime sleep that occur without warning, are not specific for narcolepsy and that they may occur in association with any disorder that leads to severe chronic sleepiness (p. S3, col 1, 1st full para). Aldrich further teaches that some patients with narcolepsy, may not experience sleep attacks. Therefore, the art teaches that symptoms of sleep disorders in general are not necessarily associated with narcolepsy and are not specific for narcolepsy. Without a teaching of how the mutations taught in the specification affect the activity of the hypocretin receptor 2 and lead to narcolepsy, the skilled artisan would not be able to predictably correlate which alterations in activity of the hypocretin receptor 2, let alone which mutations lead to such alterations, would

be associated with sleep disorders in general when the relationship between sleep disorders and narcolepsy are not well understood, as exemplified by the teachings in the prior art.

The response asserts that the term "polymorphism", while encompassing single nucleotide polymorphisms, are not limited to such and can include alterations in the genomic sequence that lead to alternative splicing and production of a hypocretin receptor that is truncated relative to wildtype. This argument has been thoroughly reviewed but was not found persuasive to overcome the rejection. Firstly, the examiner acknowledged in the previous office action that the term polymorphism encompassed different types of mutations, in both the DNA encoding as well as the hypocretin receptor 2 protein. Further, this point was made to illustrate that while the specification taught a specific type of mutation in hypocretin receptor 2 in canines, that the term was broader such that the specification does not enable the full scope of the claims. To reiterate, the mutations in the canine hypocretin receptor 2 gene taught in the specification were deletions of exon 4 or exon 6 which lead to truncated receptors. These mutations represent significant alterations in the amino acid sequence of the hypocretin receptor 2. However, the claims encompass a large number of different types of mutations, such as SNPs that could lead to single amino acid changes, whereas neither the specification nor the prior art teach either 1) how the mutations observed in canines lead to narcolepsy, or 2) which other polymorphisms of the broad scope of polymorphisms encompassed by the claims would be associated with narcolepsy or any sleep disorder, such that the skilled artisan would be able to predictably correlate which mutations would alter the hypocretin receptor 2 activity and predispose a subject to narcolepsy. Without such a teaching, the skilled artisan would have to perform a study which included screening a large number of affected and control subjects to determine which mutations or

polymorphisms would be associated with narcolepsy. The study would include a large amount of trial and error analysis, however, as exemplified by the teachings of the specification, the results of such analysis are unpredictable (specification teaches that mutations which lead to amino acid changes in the human hypocretin receptor 2 were not associated with narcolepsy or sleep disorders in general). Such experimentation is considered undue. The response asserts that the specification provides a teaching of probes and primers that could be used for detection of a predisposition to sleep disorder and that provided with the teachings in the specification, the procedures for carrying out the claimed invention become routine to one skilled in the art. These arguments have been thoroughly reviewed but were not found persuasive. The specification's teaching of probes and primers which could be used in such a study does not remedy the deficiencies in the specification or the prior art because such teachings only provide tools for the study but do not provide the skilled artisan with a teaching with respect to which mutations are predictably correlative. The teaching of probes and primers represent an invitation to experiment, without teaching which mutations are predictably correlative in keeping with the full scope of the claimed invention. While the quantity of experimentation is not the only test for enablement, in the instant case, the experimentation necessary to carry out the full scope of the claimed invention is replete with unpredictable trial and error analysis, which is considered undue.

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. A "Notice of References Cited" (PTO form 892) was inadvertently omitted from the previous office action, citing a reference from the IDS. A PTO form 892 is included in this office action, however the reference will not be provided as it was cited on applicant's IDS.

7. No claims are allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1634

Jehanne Souaya
5/14/2003